



## PATENT ABSTRACTS OF JAPAN

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(54) **NICARDIPINE HYDROCHLORIDE**  
**COMPOSITION FOR ORAL ADMINISTRATION**

## (57) Abstract:

**PURPOSE:** The titled composition containing nicardipine hydrochloride and an organic acid and capable of improving the dissolution property within a solution region at a high pH.

**CONSTITUTION:** A composition for oral administration obtained by blending nicardipine hydrochloride [2,6-dimethyl-4(3'-nitrophenyl)-1,4-dihydropyridine-

3,5- dicarboxylic acid-3-methyl ester-5- $\beta$ -(N-benzyl-N-methylamino)ethyl ester hydrochloride] with an organic acid, e.g. citric acid, tartaric acid, succinic acid, ascorbic acid, etc., and a water-soluble high polymer, e.g. methyl cellulose, hydroxypropyl cellulose, etc., at 1:0.5W0.5W3.0 ratio, adding an excipient, disintegrating agent, etc., and sufficiently mixing the ingredients. The nicardipine hydrochloride has cerebrovascular vasodilator action, coronary vasodilator action and hypotensive action by calcium antagonistic action and is useful as an ameliorant of circulatory function.

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### **JAPANESE PATENT APPLICATION (A)**

No. J62-123117

### **A NICARDIPINE HYDROCHLORIDE COMPOSITION**

### **FOR ORAL ADMINISTRATION**

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**Specification****1. Title of invention**

A nicardipine hydrochloride composition for oral administration.

**2. Patent Claims**

(1) A nicardipine hydrochloride composition for oral administration containing nicardipine hydrochloride and organic acid.

(2) A nicardipine hydrochloride composition for oral administration in accordance with Claim 1, wherein the organic acid is citric acid, tartaric acid, succinic acid, adipic acid, fumaric acid, malic acid ascorbic acid or a mixture thereof.

(3) A nicardipine hydrochloride composition for oral administration in accordance with Claim 1, wherein the formulation proportion of the organic acid is 0.5 pts. or more with respect to 1 part nicardipine hydrochloride.

(4) A nicardipine hydrochloride composition for oral administration containing nicardipine hydrochloride, (an) organic acid(s) and water-soluble polymer.

(5) A nicardipine hydrochloride composition for oral administration in accordance with Claim 4, wherein the water-soluble polymer is methyl cellulose hydroxypropyl cellulose, hydroxypropylmethyl cellulose or a mixture thereof.

(6) A nicardipine hydrochloride composition for oral administration in accordance with Claim 4, wherein the formulation proportion of the water-soluble polymer is 0.5-3.0 pts. with respect to 1 part nicardipine hydrochloride.

**3. Detailed Description of the Invention.**

This invention relates to a nicardipine hydrochloride composition for oral administration containing nicardipine hydrochloride (2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5- $\beta$ -(N-benzyl-N-methylamino) ethylester hydrochloride).

The nicardipine hydrochloride is a cardiovascular function improving agent developed as a agent having cerebrovascular dilation action, coronary artery dilation action, and hypotensive action due to calcium antagonism.

The nicardipine hydrochloride has good solubility in low liquid pH region, however, its solubility is extremely poor in high liquid pH region. Accordingly, only when the drug preparation containing nicardipine hydrochloride is retained in acidic region over sufficiently long period, the elution property from the solid preparation is good and absorption becomes possible. In other words, elution property greatly depends on the pH and the retention time in the stomach and upper intestine. The blood concentration of the drug is also markedly affected by meals, pH and the motility of the stomach and upper intestine.

One method for solving these problems has been described in Kokoku 59-48810. In other words, it is a method wherein nicardipine hydrochloride is made amorphous, thereby the elution property with intestinal fluid is improved.

The inventors of this invention completed a composition for oral administration with improved elution property in a high liquid pH region by formulating nicardipine hydrochloride with organic acid and furthermore with water-soluble polymer.

The composition for oral administration in accordance with this invention is produced as follows. Namely, an organic acid, water-soluble polymer, excipient, disintegrating agent or the like are added to nicardipine hydrochloride and the mixture is sufficiently mixed. Water or organic solvent is added to this said mixture and granulation is carried out. The formed granules may be used as product in the form of granules, or can be formed into capsule agent. Or, lubricant is added to the granules and this is formed into tablets. Moreover, the aforesaid mixture is formed into tablets by powder tableting with addition of lubricant. Wherein, the granules and tablets obtained in this way may be coated with suitable agent coating.

As the organic acid used in this invention, citric acid, tartaric acid, succinic acid, adipic acid, fumaric acid, malic acid ascorbic acid or a mixture thereof can be nominated. The formulation proportion of the organic acid is 0.5 pts. or more with respect to 1 part nicardipine hydrochloride, and the upper limit may not be established in particular, as long as the organic acid does not have physiological effect in particular or does not cause problem in agent preparation in particular.

As the water-soluble polymer, methyl cellulose hydroxypropyl cellulose, hydroxypropylmethyl cellulose and generally used water-soluble polymer for drug or a mixture of two or more species thereof can be nominated. As the formulation proportion of the water-soluble polymer, the said

polymer is used by 0.5-3.0 pts. with respect to 1 part nicardipine hydrochloride.

The reason why the elution property is improved by the addition of the said organic acid or the like, is that elution liquid penetrated into the preparation becomes low liquid pH region due to the organic acid and water-soluble polymer contained in the preparation, and this state is maintained, thereby nicardipine hydrochloride is thought to be solubilised.

As the excipient, disintegrating agent and lubricant used in this invention, species used in pharmaceutical preparation of prior art can be used. For example, as excipient, lactose, starch, mannitol, microcrystalline cellulose, calcium hydrogen phosphate or the like can be used, as disintegrating agent, carboxymethyl cellulose, carboxymethyl cellulose calcium, polyethylene glycol, starch or the like can be used, and as lubricant, magnesium stearate, talc or the like can be used. The quantity used of these additives is not limited in particular and can be suitably determined according to the object of use.

The characteristic of this invention is that without forming amorphous nicardipine hydrochloride as known in the prior art, the organic acid and furthermore water-soluble polymer or the like are formulated into nicardipine hydrochloride, thereby nicardipine hydrochloride composition for oral administration with good elution property at high liquid pH region can be extremely easily produced. Moreover, the said composition is thought to have higher stability in general than amorphous formation.

Next, this invention is explained in detail by the following Examples, however, this invention is not limited to these.

#### Example 1

##### Prescription.

nicardipine hydrochloride	20 pts.
succinic acid	20 pts.
methyl cellulose (SM-8000 ®)	20 pts.
lactose	60 pts.
corn starch	40 pts.
<u>hydroxypropyl cellulose (Nisso HPC-L ®)</u>	<u>2 pts.</u>
Total	162 pts.

##### Production method.

In accordance with the aforesaid prescription, nicardipine hydrochloride and succinic acid, lactose,

corn starch were uniformly mixed, hydroxypropyl cellulose (5 % W/V) was dissolved in ethanol and was used as binder, and ordinary wet-type granulation was carried out. The mixture was dried at 60°C overnight, thereafter, the granulated materials were classified with 20-48 mesh, and granular preparation was obtained.

**Example 2.**Prescription.

nicardipine hydrochloride	20 pts.
citric acid	20 pts.
methyl cellulose (SM-8000 ®)	20 pts.
lactose	80 pts.
microcrystalline cellulose (Avicel PH-301 ®)	60 pts.
hydroxypropyl cellulose (Nisso HPC-L ®)	3 pts.
Total	203 pts.

Production method.

In the same way as in Example 1, granular preparation of 20-48 mesh was obtained.

**Example 3.**

0.8 %W/V magnesium stearate was added to the granules obtained in Example 1, the mixture was tableted with 8 mm punch, and uncoated tablet containing 20 mg nicardipine hydrochloride per tablet was obtained.

**Example 4.**Prescription.

nicardipine hydrochloride	20 pts.
adipic acid	40 pts.
hydroxypropylmethyl cellulose (TC-5R ®)	20 pts.
hydroxypropyl cellulose (Nisso HPC-L ®)	20 pts.
lactose	50 pts.
anhydrous calcium hydrogen phosphate	10 pts.
magnesium stearate	2 pts.
Total	162 pts.

Production method.

In accordance with the aforesaid prescription, 8 mm uncoated tablet containing 20 mg nicardipine hydrochloride per tablet was obtained by powder tableting.

**Comparative Example 1.**Prescription.

nicardipine hydrochloride	20 pts.
lactose	100 pts.
corn starch	40 pts.
hydroxypropyl cellulose (Nisso HPC-L ®)	2 pts.
Total	162 pts.

Production method.

In the same way as in Example 1, granular preparation of 20-48 mesh was obtained.

**Comparative Example 2.**Prescription.

nicardipine hydrochloride	20 pts.
lactose	90 pts.
anhydrous calcium hydrogen phosphate	40 pts.
carboxymethyl cellulose calcium (ECG-505 ®)	10 pts.
magnesium stearate	2 pts.
Total	162 pts.

Production method.

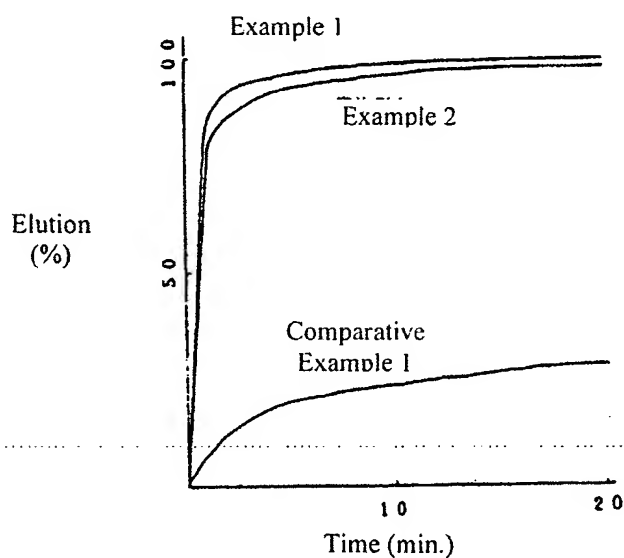
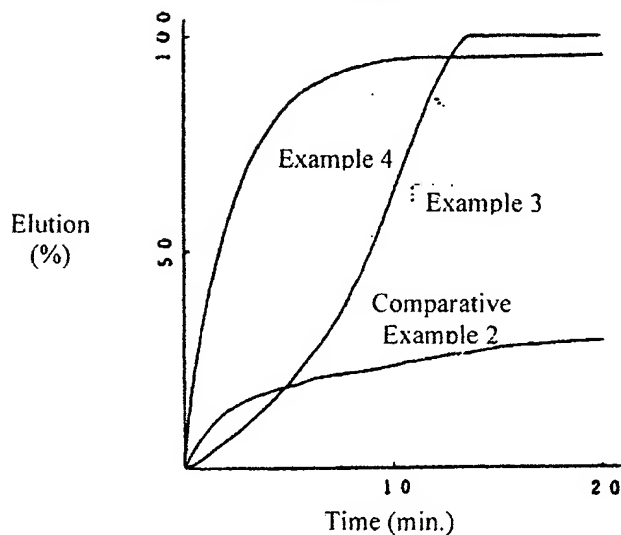
In the same way as in Example 4, 8 mm uncoated tablet containing 20 mg nicardipine hydrochloride per tablet was obtained.

The elution test of preparations obtained in Examples 1, 2, 3 and 4 and Comparative Examples 1 and 2 was carried out by Japanese Pharmacopoeia paddle method. As the test solution, pH 6.5 (0.05 M phosphate buffer solution) 900 ml was used, at which pH region the solubility of nicardipine hydrochloride is poor. The sample quantity was each preparation equivalent to 20 mg nicardipine hydrochloride. The results of elution test are shown in Figure 1 and Figure 2. As may be seen from the Figures that the compositions of this invention obtained in Examples 1, 2, 3 and 4 showed at least 95 % elution within 20 minutes despite using the test solution having poor solubility of nicardipine hydrochloride, and displayed clearly better elution compared with preparation examples by conventional methods (Comparative Examples 1 and 2).

**4. Brief Explanation of the Figures.**

Figure 1 is a figure showing the results of elution test at pH 6.5 on the granules of this invention obtained in Examples 1 and 2 and the granule obtained in Comparative Example 1.

Figure 2 is a figure showing the results of elution test at pH 6.5 on the tablets of this invention obtained in Examples 3 and 4 and the uncoated tablets obtained in Comparative Example 2.

**Figure 1.****Figure 2.**



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